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Title: Long term excess mortality associated with diabetes following acute myocardial infarction: A population-based cohort study

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Abstract

Background The long-term excess risk of death associated with diabetes following acute myocardial infarction is unknown. We determined the excess risk of death associated with diabetes among patients with ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) after adjustment for co-morbidity, risk factors and cardiovascular treatments.

Methods Nationwide population-based cohort (STEMI n=281,259 and NSTEMI n=422,661) using data from the UK acute myocardial infarction registry, MINAP, between 1st January, 2003 and 31st June, 2013. Age, sex, calendar year and country-specific mortality rates for the populace of England and Wales (n=56.9 million) were matched to cases of STEMI and NSTEMI. Flexible parametric survival models were used to calculate excess mortality rate ratios (EMRR) after multivariable adjustment. This study is registered at ClinicalTrials.gov (NCT02591576).

Results Over 1.94 million person-years follow-up including 120,568 (18.9%) patients with diabetes, there were 200,360 (28.4%) deaths. Overall, mortality was higher among patients with than without diabetes (35.8% vs. 25.3%). After adjustment for age, sex and year of acute myocardial infarction, diabetes was associated with a 72% and 67% excess risk of death following STEMI (EMRR 1.72, 95% CI 1.66-1.79) and NSTEMI (1.67, 1.63-1.71). Diabetes remained significantly associated with substantial excess mortality despite cumulative adjustment for co-morbidity (EMRR 1.52, 95% CI 1.46-1.58 vs. 1.45, 1.42-1.49), risk factors (1.50, 1.44-1.57 vs. 1.33, 1.30-1.36) and cardiovascular treatments (1.56, 1.49-1.63 vs. 1.39, 1.36-1.43).

Conclusion At index acute myocardial infarction, diabetes was common and associated with significant long-term excess mortality, over and above the effects of co-morbidities, risk factors and cardiovascular treatments.

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Contributors OA A and CPG designed the study. OA A drafted the manuscript, analysed the data and interpreted the results. TBD and MH provided scientific input. CPG provided expert clinical opinion. All the authors read, commented and approved the final version of the manuscript.

What is already known?

- Evidence suggests that the effect of diabetes on short and long term mortality persists after adjusting for demographics, co-morbidities, risk factors and treatments concurrently.
- However, it is not clear whether this effect remains after correcting for the survival of the general population.

What this study adds?

- After adjustment for case mix, risk factors and cardiovascular treatments as well as correcting for mortality from non-cardiovascular causes, diabetes was independently associated with substantial long-term excess mortality following acute myocardial infarction.
- Patients with diabetes continue to be at an elevated risk of death many years after acute myocardial infarction.

Introduction

Diabetes mellitus (DM) is a major risk factor for death following acute myocardial infarction (AMI).[1] This fact remains despite substantial international advances in the treatment and outcomes for AMI over the last decade.[2,3] Understanding the extent to which diabetes impacts on survival following AMI is of great importance because nowadays deaths following AMI are mostly due to non-cardiovascular causes.[4,5] That is, diseases which are not related to the index AMI, such as cancer, have a significant bearing on survival and could influence our interpretation of the impact of diabetes and cardiovascular disease on long-term clinical outcomes. Given that co-existent disease, aging, and the onset of new diseases among patients with AMI have a strong role in determining mortality, it is surprising that there are no large scale studies which have accounted for this.

To date, studies reporting the impact of diabetes following AMI have been historical, from small cohorts [6-8], trial populations, or have evaluated short term survival [9]. Critically, the majority have considered all-cause mortality as the clinical outcome, which does not allow an accurate evaluation of the burden of index AMI and its treatment on death. In turn, this has potential repercussions for the design and study of new treatments for patients with diabetes who have AMI. To overcome the limitations of using all-cause-mortality, some studies report cause-specific mortality addressing cardiac death rather than death to any cause. However, this may be difficult to ascertain and when available these data can be biased by misclassification.[10] An alternative method to estimate cause-specific outcomes is relative survival. Using data from the Myocardial Ischaemia National Audit Project (MINAP) which includes cases of AMI admitted to all acute hospitals in England and Wales and mortality data from the matching populace (n=56.9 million), we aimed to estimate the long-term excess mortality associated with diabetes among patients with AMI.

Methods

Patients, setting and inclusion criteria

We included all National Health Service hospitals (n=247) in England and Wales which provided care for patients (n=703,920) aged over 18 years with AMI between 1st January, 2003 and 30th June, 2013 (see Table 1a, supplementary material). For multiple admissions, we used the earliest record. Patient-level data concerning demographics, cardiovascular risk factors, medical history and clinical characteristics at the time of hospitalisation were extracted from the Myocardial Ischaemia National Audit Project (MINAP), a comprehensive registry of hospitalisations for acute coronary syndrome in England and Wales. Details of MINAP and data validation have been described previously.[11] Cases of AMI were defined as ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) according to the European Society of Cardiology (ESC), American College of Cardiology (ACC) and American Heart Association (AHA) guidelines and determined at local level by the attending consultant.[12] Cases included patients with existing type 1 or type 2 DM. The data flow for the derivation of the analytical cohort is shown in Figure 1.

Case mix

To account for case mix and cardiovascular risk, we used patient-specific information concerning demographics (age, sex), co-morbidity (previous AMI, heart failure, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), cerebrovascular disease, peripheral vascular disease (PVD), chronic renal failure, asthma/COPD, family history of coronary heart disease) and risk factors at the time of hospitalisation (systolic blood pressure, smoking, heart rate, ST-segment deviation, cardiac arrest, elevated cardiac enzyme, use of a loop diuretic) and cardiovascular treatments.

Cardiovascular treatments

Class 1 guideline recommended treatments included reperfusion treatment (primary percutaneous coronary intervention, fibrinolysis) for patients with STEMI, and coronary angiography for patients with NSTEMI.[13,14] For all patients, we considered the prescription of aspirin, β blockers, angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB), HMG Co-A reductase inhibitors (statins), thienopyridine inhibitors and cardiac rehabilitation.

Outcome

The primary outcome was excess mortality estimated using a relative survival approach. The relative survival rate was defined as the observed survival among patients with AMI divided by the expected survival of the comparable general populace of England and Wales.[15] Date of all-cause mortality was determined through linkage to Office for National Statistics mortality data using each patient's unique National Health Service number. Patients were followed-up for their vital status with censoring at the end of follow-up on 1st July, 2013 (Table 1a, Appendix) and survival time calculated from the date of AMI hospitalisation to the date of death, date of last information about vital status or the end of the study censoring period.

Statistical analyses

We used percentages to describe categorical variables and means and standard deviations or medians and interquartile ranges for continuous normally distributed and non-normally distributed variables, respectively.

We used a flexible parametric model to calculate relative survival rate ratio by dividing the observed survival of AMI patients by the expected survival of the comparable England and Wales populace matched with our cohort by age, sex, year and country. [16,17] From this, we estimated the excess mortality rate ratio (EMRR) using a baseline model which adjusted for the expected risk of death (derived from the matched general population of England and Wales as described above).[18] We built models incrementally to investigate the impact of diabetes, other co-morbidities, risk factors and cardiovascular treatments on excess mortality. Evidence of excess mortality is observed when the EMRR is greater than 1. An EMRR of 1.5, for example, for men/women indicates that men experience a 50% higher excess mortality than women. Appropriate model scale and baseline complexity for the flexible parametric models were evaluated from the Akaike information criterion (AIC) and Bayesian information criterion (BIC) on complete cases (see Table 2a and Table 2b, supplementary material). The proportional excess hazards assumption was assessed by including interaction terms between three baseline variables (age, sex, calendar year) and follow-up time, and using the likelihood ratio test on complete cases. Multiple imputation by chained equations was used to impute 10 datasets for STEMI and NSTEMI to account for missing data using methods previously defined for MINAP data, [19] and final model estimates combined according to Rubin's rules (see Table 3a, 3b and 3c, supplementary material).

All tests were two-tailed, the level of statistical significance pre-specified at 5% ($p<0.05$) and estimates derived with 95% confidence intervals (CI). Statistical analyses were performed using Stata version 13.1 (StataCorp) and R version 3.2.1.

Results

There were 281,259 (40.0%) STEMI and 422,661 (60.0%) NSTEMI of whom 65.6% were male. Mean respective ages (SD) were 65.7 (13.6) years and 71.0 (13.4) years for STEMI and NSTEMI, respectively. There were 34,348 (12.1%) STEMI and 86,220 (20.4%) NSTEMI with diabetes (Table 1). STEMI with diabetes compared with STEMI without diabetes more frequently had previous AMI (20.9 vs.10.7%), heart failure (4.0 vs. 1.6%) and chronic renal failure (5.5 vs. 1.8%). Similarly, NSTEMI with diabetes more frequently had previous AMI (34.9 vs. 22.5%), heart failure (10.5 vs. 5.8%) and chronic renal failure (11.3 vs. 4.6%), although at higher rates than among patients with STEMI. The use of a loop diuretic among patients with diabetes was higher than for patients without diabetes for STEMI (31.1 vs. 18.5%) and NSTEMI (43.8 vs. 27.4%). Table 1 also shows that guideline indicated pharmacological treatments for AMI were provided at lower rates among patients with diabetes for STEMI (all p<0 .001) and NSTEM (all p<0.001). In addition, patients with diabetes were less likely to receive reperfusion (73.1 vs. 79.0%) for STEMI. In line with the ESC guidelines [14] which recommends that patients with STEMI should receive reperfusion therapy within 60 minutes from arrival at a primary PCI centre or 90 minutes from arrival at a non-primary PCI centre, we found that a larger proportion of non-diabetic patients (98.3%, median 33.0 minutes, IQR, 18.0 to 60.0 minutes) compared with diabetic patients (97.2%, 39.0 minutes, 22.2 to 72.6 minutes) received timely reperfusion (within 90 minutes). NSTEMI diabetic patients were less likely to receive coronary angiography compared with NSTEMI non-diabetic (55.4 vs. 60.2%). We found that diabetic patients compared with non-diabetic patients were more likely to be seen by a cardiologist (64.0% vs. 58.3%) for STEMI and (62.1% vs. 53.8%) for NSTEMI and were slightly less likely to be admitted to a cardiac ward versus non-cardiac ward (83.2% vs. 86.1%) for STEMI and (47.0% vs. 48.1%) NSTEMI (Table 1).

Table 1: Baseline characteristics for STEMI and NSTEMI, stratified by diabetes

	STEMI		P value	NSTEMI		P value
	Diabetes N=34,348	No diabetes N=212,762		Diabetes N=86,220	No diabetes N=304,045	
Demographics						
Mean (SD) age, years	67.7 (12.78)	65.3 (13.7)	<0.001	71.8 (11.7)	70.8 (13.9)	<0.001
Male (%)	23,135/ 34,241 (67.6%)	150,910/211,965 (71.2%)	<0.001	54,166/86,051 (63.0%)	190,451/303,403 (62.8%)	0.071
2003-05	7,086/34,348 (20.6%)	44,735/212,762 (21.0%)	<0.001	17,614/86,220 (20.4%)	70,999/304,045 (23.4%)	<0.001
2006-08	9,430/34,348 (27.5%)	62,255/212,762 (29.3%)	<0.001	22,087/86,220 (25.6%)	82,286/304,045 (27.1%)	<0.001
2009-11	11,093/34,348 (32.3%)	69,103/212,762 (32.5%)	<0.001	30,036/86,220 (34.8%)	99,703/304,045 (32.8%)	<0.001
2012-13	6,739/34,348 (19.6%)	36,669/212,762 (17.2%)	<0.001	16,483/86,220 (19.1%)	51,057/304,045 (16.8%)	<0.001
Least deprived (1)	4,445/31,036 (14.3%)	34,353/192,349 (17.9%)	<0.001	11,001/78,832 (14.0%)	49,616/277,524 (17.9%)	<0.001
2	5,528/31,036 (17.8%)	38,667/192,349 (20.1%)	<0.001	14,070/78,832 (18.0%)	57,068/277,524 (20.6%)	<0.001
3	6,303/31,036 (20.3%)	39,100/192,349 (20.3%)	<0.001	15,947/78,832 (20.2%)	58,602/277,524 (21.1%)	<0.001
4	6,761/31,036 (21.8%)	39,090/192,349 (20.3%)	<0.001	17,556/78,832 (22.3%)	56,181/277,524 (20.2%)	<0.001
Most deprived (5)	7,999/31,036 (25.8%)	41,139/192,349 (21.4%)	<0.001	20,258/78,832 (25.7%)	56,057/277,524 (20.2%)	<0.001
White (%)	25,464/29,962 (74.1%)	176,246/187,276 (94.1%)	<0.001	67,675/78,207 (86.5%)	259,559/273,244 (95.0%)	<0.001
Co-morbidities						
Myocardial infarction*	7,190/34,348 (20.9%)	22,791/212,762 (10.7%)	<0.001	30,124/86,220 (34.9%)	68,478/304,045 (22.5%)	<0.001
Heart failure*	1,387/34,348 (4.0%)	3,413/212,762 (1.6%)	<0.001	9,014/86,220 (10.5%)	17,623/304,045 (5.8%)	<0.001
PCI*	3,084/34,348 (9.0%)	9,565/212,762 (4.5%)	<0.001	10,740/86,220 (12.5%)	23,652/304,045 (7.8%)	<0.001
CABG*	1,625/34,348 (4.7%)	4,124/212,762 (1.9%)	<0.001	9,947/86,220 (11.5%)	18,227/304,045 (6.0%)	<0.001
Cerebrovascular disease*	3,039/34,348 (8.9%)	9,780/212,762 (4.6%)	<0.001	10,890/ 86,220 (12.6%)	25,767/304,045 (8.5%)	<0.001
Peripheral vascular disease*	1,856/34,348 (5.4%)	4,978/212,762 (2.3%)	<0.001	7,283/86,220 (8.5%)	11,813/304,045 (3.9%)	<0.001
Chronic renal failure*	1,888/34,348 (5.5%)	3,736/212,762(1.8%)	<0.001	9,762/86,220 (11.3%)	13,853/304,045 (4.6%)	<0.001
Hypertension*	20,571/34,348 (59.9%)	78,050/212,762 (36.7%)	<0.001	55,664/86,220 (64.6%)	140,869/304,045 (46.3%)	<0.001
Asthma or COPD*	3,949/34,348 (11.5%)	22,341/212,762 (10.5%)	<0.001	14,266/86,220 (16.6%)	45,641/304,045 (15.0%)	<0.001
Family history of CHD*	7,495/ 34,348 (21.8%)	54,398/212,762 (25.6%)	<0.001	15,990/ 86,220 (18.6%)	64,382/ 304,045 (21.2%)	<0.001
Risk factors						
Systolic BP, mean (SD) (mmHg)	135.0 (29.3)	135.4 (28.6)	0.02	141.7 (29.0%)	141.1 (28.6)	<0.001
Systolic BP, <90mmHg	1,676/34,348 (4.9%)	8,980/212,762 (4.2%)	<0.001	2,138/86,220 (2.5%)	7,833/304,045 (2.6%)	0.392
Heart rate, mean (SD) bpm	82.7 (22.6)	77.9 (21.0)	<0.001	86.7 (23.7)	82.3 (23.7)	<0.001
Heart rate, >110 bpm	8,630/34,348 (25.1%)	45,606/212,762 (21.4%)	<0.001	21,264/86,220 (24.7%)	65,914/304,045 (21.7%)	<0.001
Current/ex-smoker*	19,444/34,348 (56.6%)	136,148/212,762 (64.0%)	<0.001	47,152/86,220 (54.7%)	174,297/304,045 (57.3%)	0.111
ST-segment deviation	30,158/33,344 (90.5%)	193,694/212,762 (93.5%)	<0.001	24,567/78,918 (31.1%)	82,373/278,745 (29.6%)	<0.001
Cardiac arrest	3,972/33,166 (12.0%)	23,366/212,762 (11.4%)	0.002	4,121/ 83,257 (5.0%)	12,487/292,759 (4.3%)	<0.001
Elevated cardiac enzymes	29,955/31,501 (95.1%)	186,244/212,762 (95.6%)	<0.001	77,641/84,291 (92.1%)	274,666/296,784 (92.6%)	<0.001

Use of a loop diuretic	8,862/28,540 (31.1%)	32,927/212,762 (18.5%)	<0.001	33,022/75,484 (43.8%)	72,344/264,528 (27.4%)	<0.001
Treatments						
Aspirin*	25,153/29,261 (86.0%)	164,393/188,095 (87.4%)	<0.001	61,684/71,784 (85.9%)	221,713/258,175 (85.9%)	<0.001
β–blockers*	6,342/7,303 (86.8%)	44,503/50,692 (87.8%)	<0.001	12,431/14,771 (84.2%)	47,020/56,113 (83.8%)	<0.001
Statin*	25,076/29,516 (85.0%)	163,584/189,165 (86.5%)	<0.001	62,248/73,784 (84.4%)	216,923/262,075 (82.8%)	0.073
ACEi or ARB*	6,699/6,967 (96.2%)	47,220/ 48,742 (96.9%)	<0.001	13,408/14,361 (93.4%)	48,891/53,285 (91.8%)	<0.001
Thienopyridine*	12,458/34,211 (36.4*)	78,469/ 212,197 (37.0%)	<0.001	29,488/85,690 (34.4%)	98,003/ 302,474 (32.4%)	<0.001
Cardiac rehabilitation*	24,349/32,153 (75.7%)	162,226/202,825 (80.0%)	<0.001	55,548/78,923 (70.4%)	204,571/ 280,308 (73.0%)	<0.001
Coronary angiography	16,888/30,468 (55.4%)	110,470/189,584 (58.3%)	<0.001	43,738/78,963 (55.4%)	167,067/277,564 (60.2%)	<0.001
Reperfusion	22,971/31,423 (73.1%)	156,207/197,631 (79.0%)	<0.001	2,526/ 62,128 (4.1%)	10,384/209,543 (5.0%)	<0.001
Care by a cardiology*	21,982/34,348 (64.0%)	143,928/246,911 (58.3%)	<0.001	53,532/86,220 (62.1%)	181,124/336,441 (53.8%)	<0.001
Admission ward						
Cardiac versus Non-cardiac ward[¥]	28,076/ 33,748 (83.2%)	206,131/239,518 (86.1%)	<0.001	40,120/ 85,432 (47.0%)	159,687/332,044 (48.1%)	<0.001
Timely reperfusion[ǂ] (≤ 90 minutes)	20,565/ 21,157 (97.2%)	164,424/167,335 (98.3%)	<0.001	---	---	---

Abbreviations: PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; CABG, coronary artery bypass graft; CAD, coronary artery disease; BP, blood pressure; *, Default imputed (we default imputed missing values as "no" if the patient was eligible to receive the medication, but was not recorded as having received it); ^, Percentages used eligible cases for treatment only in their denominator; ¥, Cardiac ward: cardiac care unit, cardiac ward; Non-cardiac ward: acute admission unit, general medical care, intensive therapy, other, died in A&E, stepdown ward; ǂ, time to reperfusion defined as the time from hospital arrival to reperfusion.

Survival

Over 1,944,194 person years at risk, the median time to death was 2.3 (IQR 0.9 to 4.2) years, 200,360 (28.4%) died. At all-time points from hospitalisation with AMI, unadjusted cumulative relative survival was significantly worse among patients with diabetes (log rank tests P<0.001) (Figure 2).

Excess mortality

Increasing age was associated with excess mortality among STEMI; those older than 85 years had a 5-fold increase in excess mortality (EMRR 5.14, 95% CI 4.85-5.45) compared with patients aged between 66 and 75 years. Excess mortality was significantly lower among males than females (EMRR 0.77, 95% CI 0.74-0.80) and for STEMI was lower among patients hospitalised between 2012 and 2013 (0.65, 0.62-0.69) compared with 2003 (Table 2a, Appendix). Similarly for NSTEMI, excess mortality increased with age; patients over 85 years had a 4-fold increased risk (EMRR 4.67, 95% CI 4.50-4.84), and males also had a lower risk of excess mortality (EMRR 0.95, 0.92-0.97). Excess mortality was significantly lower in the recent cohort (2012-13) (EMRR 0.55, 95% CI 0.52-0.59).

Effect of diabetes on excess mortality

After adjustment for age, sex and year of diagnosis, diabetes was associated with a 72% higher risk of excess mortality (EMRR 1.72, 95% CI 1.66-1.79) for STEMI and a 67% higher risk of excess mortality for NSTEMI (EMRR 1.67, 95% CI 1.63-1.71) (Table 2). For STEMI, the effect of diabetes remained despite incremental adjustment for other co-morbidities (EMRR 1.52, 95% CI 1.46-1.58), risk factors (1.50, 1.44-1.57) and cardiovascular treatments (1.56, 1.49-1.63) (Figure 3). This was also evident for NSTEMI, whereby other co-morbidities (EMRR 1.45, 95% CI 1.42-1.49), risk factors (EMRR 1.33, 95% 1.30-1.36) and cardiovascular treatments (1.39, 1.36-1.43) only modestly attenuated the long-term effect of diabetes on excess mortality (Figure 3). The effect of diabetes on excess mortality remained stable between 2003 - 2013 for STEMI (1.39, 1.13-1.71 vs. 1.63, 1.25-2.13) and NSTEMI (EMRR, 95% CI 1.35, 1.22-1.49 vs. 1.31, 1.07-1.61) (Figure 4). Similarly, the effect was not dissimilar by diabetic group according to: no treatment (newly diagnosed), dietary control, oral medications, insulin, and insulin and oral medications combined for STEMI (EMRR, 95% CI 1.32, 0.97-1.81), 1.33 (1.21-1.46), 1.51 (1.42-1.60), 1.88 (1.74-2.04) and 1.95 (1.49-2.55) and NSTEMI 1.04 (0.83-1.30), 1.17 (1.11-1.24), 1.28 (1.24-1.33), 1.82 (1.75-1.90) and 1.48 (1.30-1.68), respectively (Table 4a, Appendix).

Other factors associated with excess mortality

For STEMI, long-term excess mortality was associated with co-morbidity, including previous AMI (EMRR 1.25, 95% CI 1.19-1.32), heart failure (1.32, 1.22-1.43), CABG (1.19, 1.07-1.33), cerebrovascular disease (1.47, 1.39-1.55), peripheral vascular disease (1.44, 1.32-1.56), chronic renal failure (1.50, 1.39-1.62) and asthma/COPD (1.11, 1.06-1.17). A significant reduction of excess mortality was found among patients who had a family history of cardiovascular disease (EMRR 0.76, 95% CI 0.71-0.81). STEMI with a systolic blood pressure ≤90mmHg (EMRR 2.20, 95% CI 2.07-2.32), heart rate >110 bpm (1.70, 1.61-1.80),

who smoked (1.05, 1.01-1.09), had an elevated cardiac troponin (1.16, 1.07-1.26) and were taking a loop diuretic (1.34, 1.28-1.40) at their time of hospitalisation had significantly elevated risk of excess mortality. The strongest determinant, however, was cardiac arrest (EMRR 6.04, 95% CI 5.80-6.28). We found that patients who had a cardiac arrest after admission to hospital had higher excess mortality compared to those who had a pre-hospital cardiac arrest , for STEMI (EMRR, 95 CI% 6.40, 6.13- 6.67 vs. 3.64, 3.40-3.89) and NSTEMI (EMRR, 95 CI% 6.78, 6.51-7.05 vs. 4.69 4.34-5.07). Excess mortality was significantly reduced among STEMI who received aspirin (EMRR 0.56, 95% CI 0.52-0.60), β-blockers (0.51, 0.48-0.54), statins (0.43, 0.40-0.46), ACEI/ARBs (0.50, 0.46-0.53) and thienopyridine inhibitors (0.88, 0.79-0.97). Cardiac rehabilitation (EMRR 0.24, 95% CI 0.23-0.25) and reperfusion therapy (0.83, 0.79-0.86) were also significantly associated with reduced excess mortality (Figure 3).

For NSTEMI, excess mortality was significantly associated with previous AMI (EMRR 1.25, 95% CI 1.22-1.29), heart failure (1.32, 1.28-1.37), cerebrovascular disease (1.28, 1.24-1.31), peripheral vascular disease (1.41, 1.37-1.47), chronic renal failure (1.43, 1.38-1.48) and asthma/COPD (1.17, (1.13-1.20). Excess mortality was significantly reduced among NSTEMI with a family history of cardiovascular disease (EMRR 0.68, 95% CI 0.65-0.71). NSTEMI with a systolic blood pressure ≤90mmHg (EMRR 1.93, 95% CI 1.84-2.02), heart rate >110 bpm (1.35, 1.31-1.39), ST segment deviation on the electrocardiograph (1.31, 1.28-1.34), elevated cardiac troponin (2.85, 2.65-3.07) and the use of loop diuretic (1.77, 1.72-1.81) at hospitalisation, had significantly higher risk of excess mortality. As with STEMI, the strongest determinant of excess mortality among NSTEMI was cardiac arrest (EMRR 7.06, 95% CI 6.82-7.30). All guideline-indicated medications were significantly associated with reduced excess mortality, including aspirin (EMRR 0.51, 95% CI 0.50-0.53), β-blockers (0.57, 0.56-0.59), statins (0.47, 0.46-0.49), ACEI/ARBs (0.62, 0.60-0.64) and thienopyridine inhibitors (0.86, 0.83-0.90). For those NSETMI who received coronary angiography (EMRR

0.17, 95% CI 0.17-0.18) and who had cardiac rehabilitation (0.48, 0.47-0.50), the risk of excess mortality was significantly reduced (Figure 3).

Table 2: Excess mortality rate ratios stratified by STEMI and NSTEMI

	STEMI	**NSTEMI**
	EMRR (95% CI) N= 263,159	EMRR (95% CI) N= 399,370
Model 1 = Baseline model + diabetes		
Diabetes	1.72 (1.66-1.79)*	1.67 (1.63-1.71)*
Model 2 = Baseline model + diabetes + co-morbidities		
Diabetes	1.52 (1.46-1.58)*	1.45 (1.42-1.49)*
Model 3=Baseline model + diabetes + comorbidities + risk factors		
Diabetes	1.50 (1.44-1.57)*	1.33 (1.30-1.36)*
Model 4 = Baseline model + diabetes + co-morbidities + risk factors + treatments		
Diabetes	1.56 (1.49-1.63)*	1.39 (1.36-1.43)*
Co-morbidities		
Previous AMI	1.25 (1.19-1.32)*	1.25 (1.22-1.29)*
Heart failure	1.32 (1.22-1.43)*	1.32 (1.28-1.37)*
Previous PCI	0.99 (0.90-1.09)	0.83 (0.79-0.88)*
Previous CABG	1.19 (1.07-1.33)*	0.97 (0.93-1.01)
Cerebrovascular disease	1.47 (1.39-1.55)*	1.28 (1.24-1.31)*
PVD	1.44 (1.32-1.56)*	1.41 (1.37-1.47)*
Chronic renal failure	1.50 (1.39-1.62)*	1.43 (1.38-1.48)*
Asthma or COPD	1.11 (1.06-1.17)*	1.17 (1.13-1.20)*
Family history of CHD	0.76 (0.71-0.81)*	0.68 (0.65-0.71)*
Risk Factors		
Systolic BP>90mmHg (reference)	1.00	1.00
Systolic BP≤90mmHg	2.20 (2.07- 2.32)*	1.93 (1.84-2.02)*
Current/ex-smoker	1.05 (1.01-1.09)*	1.02 (1.00-1.04)
Heart rate ≤110bpm (reference)	1.00	1.00
Heart rate >110bpm	1.70 (1.61-1.80)*	1.35 (1.31-1.39)*
ST-segment deviation	1.00 (0.94-1.05)	1.31 (1.28-1.34)*
Cardiac arrest	6.04 (5.80-6.28)*	7.06 (6.82-7.30)*
Elevated cardiac enzyme	1.16 (1.07-1.26)*	2.85 (2.65-3.07)*
Use of a loop diuretic	1.34 (1.28-1.40)*	1.77 (1.72-1.81)*
Treatments		
Aspirin	0.56 (0.52-0.60)*	0.51 (0.50-0.53)*
β–blockers	0.51 (0.48-0.54)*	0.57 (0.56-0.59)*
Statin	0.43 (0.40-0.46)*	0.47 (0.46-0.49)*
ACEI or ARB	0.50 (0.46-0.53)*	0.62 (0.60-0.64)*
Thienopyridine	0.88 (0.79-0.97)*	0.86 (0.83-0.90)*
Cardiac rehabilitation	0.24 (0.23-0.25)*	0.48 (0.47-0.50)*
Coronary angiography	-	0.17 (0.17-0.18)*
Reperfusion	0.83 (0.79- .86)*	-

Abbreviations: PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; CABG, coronary artery bypass graft; CAD, coronary artery disease; BP, blood pressure; * Significance level <0.05; -, the procedure was not performed, Baseline model adjusted for age, sex and year.

Discussion

This study of more nearly three quarters of a million patients with nearly 2 million person years at risk over a 8.4 year follow up period shows a strong and highly significant association between diabetes and long-term excess mortality following AMI. The positive association between diabetes and excess death was evident for cases of STEMI and NSTEMI, and attenuated only marginally by incremental adjustment for co-morbidity, risk factors and cardiovascular treatments. Our study provides robust evidence that diabetes is a significant long-term population burden among patients who have had AMI.

Patients with diabetes more often presented with NSTEMI, and more frequently were co-morbid. At presentation, they were more ill – being more likely to have cardiac arrest and features of cardiogenic shock. We found that invasive cardiac procedures, such as primary PCI and coronary angiography were performed less frequently among those with diabetes and, at time of discharge from hospital, they were less frequently prescribed evidence-based pharmacological therapies. Patients with diabetes also more frequently had a loop diuretic, which likely reflected their nearly 2-fold higher prevalence of heart failure. Notably, these findings were consistent across STEMI and NSTEMI.

Relative survival was worse among patients with diabetes compared to the non-diabetic. Moreover, survival was worst at all time points among NSTEMI with diabetes, and best among patients with STEMI and no diabetes. This divergence in survival occurred immediately following AMI and persisted until the end of the study over 8 years later. We found that the impact of diabetes on STEMI was not as severe as that of NSTEMI without diabetes. NSTEMI, were consistently more co-morbid; for example, they were on average 5 years older and much more likely to have in addition to diabetes, renal failure, heart failure, asthma/COPD, peripheral vascular disease, cerebrovascular disease and hypertension.

Co-morbidity, risk factors and cardiovascular treatments all contributed to clinical outcomes following AMI. Yet, even when we comprehensively adjusted for these factors, our findings of the substantial impact of diabetes on death following STEMI or NSTEMI remained. That is, there was significant and continuing excess risk of death associated with diabetes over and above case mix and treatments used in the management of AMI. Moreover, the impact of diabetes on excess mortality did not change over the period of study, suggesting that advances in the management of AMI have not fully addressed the mortality associated with diabetes.

To our knowledge, this is the first large scale investigation of the excess mortality associated with diabetes following AMI. Although, the role of diabetes in the development of, and outcome from, AMI is known,[8,20] no other study has measured at a population level the excess risk specifically attributable to AMI and diabetes after adjustment for co-morbidity, risk factors and treatments. To undertake this, we used a relative survival approach matching cases of hospitalised AMI in England and Wales between 2003 and 2013 by year, country, age and sex to populace mortality data. By accounting for deaths that were not attributable to the index AMI, our study allows greater insight into the specific effects of AMI and diabetes on death.

Others have found that diabetes confers a survival disadvantage following AMI. An electronic health record study of 1.5 million patients with AMI found that diabetes was independently associated with 7% increased risk of in-hospital mortality.[21] In a previous study, we investigated survival trends at 18 months among AMI patients with and without diabetes, with similar findings of higher rates of death among patients with diabetes and no long-term improvements in outcomes.[8] At 20 years of follow-up the adverse impact of diabetes on survival after AMI remains unchanged.[6,22] These research cohorts were,

however, small, historical and they did not study causes of death. Given recent evidence suggesting that for patients with an index cardiac event, death at long-term follow-up is predominantly determined by non-cardiovascular factors,[4,5] we performed relative survival analyses to mitigate possible over-inflation of the effect of diabetes on death associated with AMI.

Despite adjustment for case mix, risk and treatments, the impact of diabetes on excess mortality persisted. This suggests that additional factors are at play, which if identified and addressed could improve survivorship among this vulnerable group. We did not have data for medications during follow-up, and it is possible that drug adherence, compliance and/or persistence patterns were different between patients with and without diabetes.[23] In addition, patients with diabetes and AMI present with and more rapidly accumulate micro- and macro vascular complications and we speculate that this contributes to their more rapid demise. We also noted that on hospitalisation, patient with diabetes had much higher rates of heart failure and prescription for loop diuretics suggesting that their presentation was complicated by clinical left ventricular dysfunction – a critical prognostic marker.[24] Further, a number of studies have debated the importance of glycaemic control during hospitalisation for AMI, and our recent work suggests that admission glucose has a stronger mortality effect on NSTEMI than STEMI survival, which was intensified by antecedent diabetes.[25]

Whilst this study has strengths, including the size and quality of the data sets (there are no other databases of comparable size, coverage and quality which include all hospitals within a country), there were limitations. We did not have information about the treatment of diabetes, which if available could have cast light on the real world comparative efficacies of diabetic medications on survival following AMI as well as their compliance rates. Even though relative survival and excess mortality are novel concepts for the evaluation of

cardiovascular outcomes,[15] these techniques are well established in cancer epidemiology and are particularly important when population mortality rates derived from national life tables are unable to account for deaths not due to the condition of interest. Mortality estimates of the general population were obtained from national life tables that are stratified by age, sex and calendar year. Unfortunately, information on diabetes within these life tables was not publicly available in the UK. The prevalence of AMI and diabetes among the general population may have, therefore, overinflated our survival estimates.[17,26] Furthermore, relative survival for individuals with diabetes may tend to be overestimated because this group of patients experience a higher general all-cause mortality than the general population. Missing data could have biased the estimates. However, we used multiple imputation algorithms to minimise this bias. The corresponding sensitivity analyses confirmed consistent results irrespective of the method adopted (see supplement). It is probable that factors beyond the hospital stay (such as drug adherence and primary care visits) may also have influenced survival. Finally, the relative survival models disclosed show many important associations, but cannot provide evidence for causation.

In conclusion, data from the largest AMI registry provides evidence to suggest that diabetes was common at time of AMI and associated with significant long-term excess mortality, over and above the effects of co-morbidity, risk factors and cardiovascular treatments. Future research should concentrate on reducing the long-term burden of cardiovascular disease among patients with diabetes.

Figures

Figure 1: STROBE diagram of exclusion of cases from the Myocardial Ischaemia National Audit Project (MINAP) dataset, to derive the analytical cohort.

Figure 2: Unadjusted cumulative relative survival with 95% CIs for STEMI and NSTEMI, stratified by diabetes

Figure 3: Impact of co-morbidity, risk factors and treatments on excess mortality for STEMI (A) and NSTEMI (B). Model1: Baseline model + Diabetes, Model2: Model1 + Comorbidities, Model3: Model2 + Risk factors, Model 4: Model3 + Treatment.

Figure 4: Impact of diabetes on excess mortality stratified by year of diagnosis for STEMI (A) and NSTEMI (B)

Appendix

Table 1a: Years of diagnosis and years of follow-up

Table 2a: Choice of scale and baseline complexity for the full model, STEMI cohort.

Table 2b: Choice of scale and baseline complexity for the full model, NSTEMI cohort.

Table 3a: Baseline and clinical characteristics for the 2003-2013 AMI cohort with missing levels

Table 3b: Excess mortality rate ratios stratified by age, sex, calendar year and country with 95% CIs using complete case analysis.

Table 3c: Excess mortality rate ratios stratified by co-morbidity, risk factors and treatments with 95% CIs using complete case analysis.

Table 4a: Excess mortality rate ratios stratified by co-morbidity, risk factors and treatments using imputed data, diabetes type treatment.

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